Respecting Hartley et al., applicants aver that no conclusion can be drawn as to whether the R isomer would enjoy any advantage over racemic albuterol in terms of side effects. However, the skilled artisan would have nevertheless expected the side effect profile of the racemate to be the additive result of the individual isomers and thus he/she would have expected the different isomers to exhibit varying side effect profiles.

As for Buckner et al., applicants point to the fact that the authors concluded that both isomers of albuterol were equally selective for tracheal tissue over atrial tissue and go on to argue that since the authors did not examine racemic albuterol, no conclusion can be drawn as to any potency advantage of a single pure R isomer vs the racemate. However, what appears important here is that from the data presented by Buckner et al., the skilled artisan would have appreciated that (-) salbutamol was effective in relaxing bronchial smooth muscle which clearly supports the Examiner's position that it would have been obvious to do what applicants are claiming.

Respecting Hawkins, the Examiner notes that the authors clearly indicate that the (-) isomer of salbutamol is more active than the (+) isomer and was "significantly" more active than the racemic and that such results are "In agreement with the general finding that a racemic drug's activity lies between those of the two enantiomers"(page 857, column 1, lines 4 and 5 of the text under Fig. 1). Applicants argue that no conclusion can be drawn from this study as to

tissue selectivity. However, such conclusions are clearly provided for by Buckner et al. as discussed above.

Applicants also argues that there are only two situations in which the instantly claimed invention could be found to have been obvious, "(1) a teaching that [R-albuterol] is more than twice as potent as the racemate [which would indicate that the S-isomer's activity is antagonistic to the R-isomer's potency]; or (2) a teaching that fewer side effects are associated with the R isomer.". However, for the reasons presented above, the Examiner maintains that there is a third possibility, namely, a teaching of the effectiveness and side effect profile of the racemate which would have led the skilled artisan to expect that the individual isomers possess varying degrees of these properties such that when quantitatively combined would equal the activity of the racemate. Applicants also argue that the prior art is silent as to what the skilled artisan ought to expect. However, it is maintained that the skilled artisan would have expected that a racemic drug's activity lies between those of the two enantiomers as highlighted by Hawkins. Further, applicants offer that one skilled in the art would be, at least, confused by the cited references. However, the results reported by the various authors, while not supportive of the fact that the activities are absolutely predictable, would have nevertheless provided at least a reasonable expectation of successfully employing R-albuterol in the manner claimed. In any event, since it has been established that the racemic mixture and isomeric forms of albuterol have been used or tested as

bronchodilators in the treatment of asthma, the use of compositions containing the claimed isomer in the treatment of asthma is clearly rendered obvious, notwithstanding the inconsistency of the prior art on this point.

It is also noted that applicants argue that a process for the resolution of racemic albuterol would inevitably produce R-albuterol in less than 50% yield which would not have motivated the skilled artisan to prepare and administer this isomer. Such a yield, however, is not seen to be of the determinative importance as urged since it fails to take into account the other factors that would be considered such as the efficacy and safety of the drug.

Applicants further renew their argument based upon the declaration of Gunnar Aberg that there was no teaching in the art that the use of pure R-albuterol enjoyed any advantage in diminution of side effects. However, as previously discussed, the skilled artisan would have expected the activities exhibited by the individual isomers to be components of that exhibited by the racemate and would have expected one isomer to be more or less active than the other. The fact that applicants have identified which of the two isomers produces the least side effects is not seen to be a patentable step.

Claims 6, 8 and 15-18 remain rejected under 35 U.S.C. § 103 as being unpatentable over Brittain et al., Hartley et al., Buckner et al. and Hawkins as

applied to claims 1-5 above in further view of Muittari et al., each of record, for the reasons of record as maintained in the last Office action.

Applicants' argument that Muittari et al. fail to supply a teaching regarding the advantage of the use of the R isomer in diminishing side effects is noted but not deemed persuasive as it would have been expected by one skilled in the art that one of the two enantiomers would possess a different degree of activity from the other.

Respecting the declaration of Dr. Aberg filed July 23, 1993, the Examiner is in agreement with applicants at page 10 of their remarks that the declaration is accepted for what it teaches, namely, "that a person of skill in the art would accept the studies in guinea pig trachea and the experiments of Chapman et al. and Morley et al....as predictive of a higher therapeutic index for R-albuterol.". However, the declaration, as well as newly cited GB 2,255,503 which was published subsequent to applicants' filing date and which shows what applicants are claiming, cannot be afforded the significance urged because such would have been expected by the skilled medical artisan given, for example, the teachings of Hawkins that the (-) isomer of salbutamol is significantly more active than the racemate on guinea pig tracheal tissue.

Finally applicants have averred that the decision *In re Adamson* should not be extended to stand for the proposition that a new method for using an isomer is unpatentable "particularly where, as here, the method unexpectedly provides an

improved therapeutic ratio."(applicants' remarks at page 12). Also, it is argued that applicants' have gone far beyond the evidence of enhanced potency in *Adamson* in showing a reduction of unspecified side effects. However, as previously expressed, it is not seen that an unexpectedly better therapeutic ratio has been demonstrated nor is it considered unobvious that one isomer would be more or less prone to cause side effects.

Thus, for these reasons, the claims are deemed to remain properly rejected.

None of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ray Henley whose telephone number is (703) 308-4652.

RAYMOND L. HENLEY III
PRIMARY EXAMINER
GROUP 120 - ART UNIT 125

Henley: rjh
February 24, 1994

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/163,581	12/7/93	BARBERICH	SPC8905

EXAMINER	
R. Henley	
ART UNIT	PAPER NUMBER
1205	37

DATE MAILED:

EXAMINER INTERVIEW SUMMARY RECORD

All participants (applicant, applicant's representative, PTO personnel):

(1) Phil Hansen (3)
(2) RAY Henley (4)

Date of interview 03 MAY 1994

Type: ☐ Telephonic ☒ Personal (copy is given to ☐ applicant ☒ applicant's representative).

Exhibit shown or demonstration conducted: ☐ Yes ☒ No. If yes, brief description:

Agreement ☒ was reached with respect to some or all of the claims in question. ☐ was not reached.

Claims discussed: all

Identification of prior art discussed: all

Description of the general nature of what was agreed to if an agreement was reached, or any other comments: AGREED THAT METHODS F TREATING A CHRONIC ASTHMA PATIENT W/ Rc-)isomer of Albuterol, w/d be patentable sine data shows that airway hyperactivity is unexpectedly avoided in such patients. However, support for such chronic treatment is questioned in light of the specification. Composition aims would REMAIN REJECTED

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendments which would render the claims allowable is available, a summary thereof must be attached.)

Unless the paragraphs below have been checked to indicate to the contrary, A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW (e.g., items 1–7 on the reverse side of this form). If a response to the last Office action has already been filed, then applicant is given one month from this interview date to provide a statement of the substance of the interview.

☒ It is not necessary for applicant to provide a separate record of the substance of the interview.

☐ Since the examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action.

Examiner's Signature

PTOL-413 (REV. 1-94)

DLEV012274

8PC8905

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Barberich et al.

Serial No.: 08/163,581 Group Art Unit: 1205

Filed: December 7, 1993 Examiner: R. Henley

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE (R)-ALBUTEROL

CERTIFICATE OF TRANSMISSION

I hereby certify that this correspondence is being facsimile transmitted to the Patent and Trademark Office:

on May 12, 1994

Philip E. Hansen

Signature

Philip E. Hansen

Typed or printed name of person signing certificate

To: Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

This is in response to the office action of February 25, 1994, to which response is required by May 25, 1994; this response is therefore timely filed. The response, in the first part, addresses the issues raised in the office action of February 25 and, in the second part, responds to issues raised in the interview graciously granted by Examiner Henley with applicants' undersigned agent on May 3, 1994.

AMENDMENT

Please cancel claims 15 to 18.

Please amend claim 1 as follows:

1. (Amended) A method of treating asthma in an individual with albuterol, while reducing side effects associated with chronic administration of racemic albuterol, comprising administering to the individual a quantity of an

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optically pure R(-) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects, said R isomer being substantially free of its S(+) isomer.

REMARKS

Claims 1-6, 8 and 15-18 were present in the application as filed under 37 CFR 1.62. Claims 15 to 18 are canceled by amendment above. Claims 1-6 and 8 are therefore pending in the application.

In the office action of February 25, claims 1-6 were rejected under 35 USC §103 as obvious over Muittari et al. (Chem. Abs. 89:12359m). As explained in the Preliminary Remarks submitted December 7, 1993, Muittari deals strictly with the effects of racemic albuterol. Applicants do not believe Muittari could suggest anything about the advantages attendant upon the use of a single enantiomer.

Claims 1-6 and 8 were also rejected over Brittain et al., Hartley et al. and Buckner et al. As explained in the interview of May 3, and in the Preliminary Remarks of December 7, each of the Brittain, Hartley and Buckner references discusses the pharmacology of the individual enantiomers, but none suggests any advantage in diminution of side effects to be gained from the use of the pure R enantiomer, which is the substance of applicants' claimed invention.

Applicants have found that when isolated guinea pig tracheal muscle preparations were subjected to graded doses of a spasmogen, the contractile response to the spasmogen was significantly increased in bronchial tissue strips that had been incubated with S-albuterol. No such effect was seen in the tissues that had been incubated with R-albuterol. They concluded that the increased sensitivity to spasmogens from treatment with S-albuterol was due to a direct effect on

bronchial smooth muscle.

Subsequent to the filing of applicants' original application, Morley et al. and Chapman et al. (references provided with the response of February 16, 1993) independently disclosed that the S isomer in bronchial tissue causes a hypersensitivity to allergen. British patent application 2,255,503, filed (by Morley and Chapman) more than a year after applicants' '262 application, makes a similar disclosure and presents claims very similar to applicants'.

After reviewing the foregoing issues in the interview of May 3, the examiner indicated that he felt there might be patentable subject matter related to avoidance of side effects that show up on chronic medication with racemic albuterol. He felt that a claim in the format of amended claim 1 above could be allowable if two issues could be resolved: (1) whether support exists in the specification for the restriction of the method to avoidance of side effects in chronic therapy and (2) whether Dr. Aberg's showing of July 23, 1993, is commensurate with the original disclosure.

The first of these concerns is addressed in the accompanying declaration under 37 CFR 1.132 of T. Scott Johnson, M.D. Dr. Johnson explains that although the term "chronic" does not appear in the specification as originally filed, the person of ordinary skill in the art would expect that albuterol would be given chronically, since that is the common mode of therapy. Moreover, the concept of chronic administration is implicit in the description of modes of administration that is found in the specification. In particular, on page 4 in the paragraph extending from line 4 to line 13, and page 5, line 6 to line 9, the prophylactic therapy described makes medical sense only if chronic administration is intended.

As to the second point, applicants' agent believes that

the seminal case on the question of the correspondence between a showing and the scope of the original disclosure that he and the examiner were seeking is *In re Zenitz* (142 USPQ 158). Zenitz was claiming compounds and applicants are claiming a method of use, so the analogy is not perfect, but the reasoning appears apposite. In *Zenitz* the applicant had disclosed that the compounds sought to be patented were useful as sedatives and hypotensive agents, but had not discussed any separation between sedation and hypotensive effects as an advantage of his compounds. In support of the unobviousness of the compounds, he provided an affidavit showing the unexpected separation of hypotensive and sedative effects in certain of these compounds. The examiner held, and the Board of Appeals affirmed, that since the separation of effects was not originally disclosed, Zenitz could not rely on that in his showing.

However, the CCPA reversed the decision of the Board of Appeals on the basis that the unexpected utility, although not specifically disclosed, would nevertheless flow from the disclosed utility. Applicants believe that the same reasoning applies to their situation: applicants did not specifically disclose airway hyperreactivity as a side effect to be avoided by the use of the pure R isomer; however, airway hyperreactivity is certainly a side effect and avoiding airway hyperreactivity could be said to reasonably flow from the disclosure of avoiding side effects. Thus applicants believe that the declaration of Dr. Gunnar Aberg submitted July 23, 1993, and the articles by Chapman and Morley reinforcing that declaration, provide appropriate support for the claims to "avoiding side effects" consistent with the holding of the CCPA in *Zenitz*.

The CCPA in *Zenitz* distinguished their decision from *In re Herr* (134 USPQ 175). In *Herr*, the utility disclosed for

the compounds sought to be patented was solely as chemical intermediates and the affidavit proffered by Herr alleged utility as anabolic and androgenic agents. The court found that the anabolic and androgenic utility would not flow from their disclosed utility as intermediates. Applicants believe that the situation in the present case is analogous to Zenitz and can be distinguished from Herr on the same basis as that provided by the CCPA.

In light of the foregoing amendment, declaration and explanation, it is believed that the application is in condition for allowance and such is respectfully requested.

Respectfully submitted,

Philip E. Hansen
Agent for Applicants
Registration No. 32,700

Dated: May 12, 1994

HESLIN & ROTHENBERG, P.C.
5 Columbia Circle
Albany, New York 12203-5160
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Put #38

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Timothy J. Barberich and James W. Young

Applicant's Docket No.: SPC89-05 Group Art Unit: 1205

Filed: December 7, 1993 Examiner: R. Henley III

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

DECLARATION UNDER 37 C.F.R. §1.132

To: Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

I, T. Scott Johnson, declare:

1. I reside at 415 Nashwatuc Road, Concord, Massachusetts.

2. I earned a Bachelor of Science degree from the University of Alabama in 1969 and an M.D. degree from the University of Alabama School of Medicine in 1973. I am certified by the American Board of Internal Medicine with a subspecialty in Pulmonary Disease. I have been a Clinical and Research Fellow in Pulmonary Disease at the University of Colorado Medical Center, and, until 1991 I was Assistant Professor of Medicine at Harvard Medical School, where I was an Attending Consultant in Pulmonary Disease.

3. I am the author of 16 original articles, 8 review articles and a textbook on subjects relating to pulmonary disease.

4. I am presently a Managing Partner of Medical Portfolio Management, Inc., in Cambridge, Massachusetts. In this capacity, I have been retained by Sepracor, Inc.

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(assignee of the above-identified application) as a paid consultant on an hourly basis. My compensation from Sepracor is unaffected by any change in status of the above-identified application, and I will not benefit financially from issuance of a patent thereon.

5. I have reviewed and do understand the contents of the above-identified application, which is directed to a method for treating asthma while avoiding the side effects associated with racemic albuterol by using the pure R-enantiomer of albuterol. As a result of my knowledge and experience I make the following observation:

The term "chronic" does not appear in the specification. However, the concept of chronic administration is implicit in the description of modes of administration that is found in the specification. In particular, on page 4 in the paragraph extending from line 4 to line 13, the concepts of the two modes of therapy (acute and chronic) are discussed. In the first mode (acute) the albuterol is administered "after onset of asthma". In the second, albuterol is administered "prophylactically, that is, before the bronchiospasm (sic) begins in an asthma attack, to prevent its occurrence."

Asthma is defined (Webster's Medical Desk Dictionary, 1986 edition) as "a condition often of allergic origin that is marked by continuous or paroxysmal labored breathing accompanied by wheezing, by a sense of constriction in the chest, and often by attacks of coughing or gasping". To be noted is the distinction between asthma (a condition or disease state) and an asthmatic attack (an acute episode of coughing, wheezing or gasping), which often accompanies the general disease state. Asthmatic attacks can be treated acutely; asthma is treated chronically.

Albuterol is, in the presently claimed invention, intended to be administered to "an individual who has asthma" (line 5 to 6). Since the patient has asthma (i.e suffers from a disease state), and treatment is to be prophylactic, treatment would have to be chronic. If the treatment were not chronic, cessation of administration might or might not lead to an immediate attack, but it would certainly lead to

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reestablishment of the disease condition.

Thus, although the term "chronic" is not used, its implication is clear in the description of prophylactic therapy. Indeed, since one is commonly not able to predict the onset of an acute attack, and since current practice in the treatment of asthma favors the treatment of the underlying disease state, many patients are treated chronically. Thus the person of skill in the art would understand that the application was referring to chronic therapy when it speaks of either prophylactic or periodic administration.

That the concept of chronic medication is envisioned is further supported by the disclosure on page 5, line 6 to line 9, regarding oral therapy. An oral regimen of "1 to about 8 mg two to four times daily" would not make sense as acute therapy.

6. I further declare that all statements of the foregoing declaration made of my own knowledge are true and that all statements made upon information and belief are believed true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above identified application or any patent issuing thereon.

Signed by me this 11th day of May, 1994.

T. Scott Johnson

[illegible]
May 11, 1994

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S.N. 14 12C

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JOHN T. JOHNSON
PHILIP E. HANSEN, PH.D.
PATENT AGENT

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Date: May 12, 1994

From: Philip E. Hansen

Heslin & Rothenberg, P.C.
Fax No.: (518) 452-5579

No. of Pages: 9 (Including this Cover Sheet)

Re: Our Ref.: 0701.027B

To: Examiner Raymond J. Henley, III (Group Art Unit 1205)

Fax No.: 1-703-308-4556

Message:

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Date: July 13, 1994

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Fax No.: (518) 452-5579

No. of Pages: 5 (Including this Cover Sheet)

Re: Our Ref. 0701.027B

To: Examiner Raymond J. Henley, III (Group Art Unit 1205)

Fax No.: 1-703-308-4556

Message:

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[redacted]

Art Unit 121 Paper No. 22

MAILED

Appeal No. 629-61 JAN 28 1987 SPT

HEARD:
November 24, 1986

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BOARD OF PATENT APPEALS
AND INTERFERENCES

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte Giorgio Ferrari
and
Vittorio Vecchietti

Application for Patent filed October 14, 1982, Serial No. 434,362; a Continuation-in-Part of Serial No. 371,428 filed April 23, 1982; a Continuation of Serial No. 123,770 filed February 20, 1980, Abandoned. Process for the Separation of the Two Optical Isomers of Moprolol and Pharmaceutical COmpositions of the Laevorotatory Antipode Thereof.

Arthur R. Crawford et al. for appellants.

Primary Examiner - Richard A. Schwartz.

Before Milestone, Goldstein and Downey, Examiners-in-Chief.

Milestone, Examiner-in-Chief.

This is an appeal from the final rejection of claims 1 to 3, which are all of the claims in the case.

The claims are reproduced below:

1. A pharmaceutical composition for treating hypertension without causing cardiac depression which comprises a therapeutically effective amount of the laevorotatory form of moprolol or of a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier.

2. A method for a long-term treatment of hypertension comprising administering to a hypertensive patient requiring said treatment an effective amount of the laevorotatory form of moprolol or of a pharmaceutically acceptable salt thereof.

3. A pharmaceutical composition for treating hypertension without causing cardiac depression which comprises from 5 to 250 mg of the laevorotatory form of moprolol or of a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier.

The following is the art relied upon by the examiner:

Wilhelm et al. (Wilhelm)	3,483,221	Dec. 9, 1969
Crowther et al. (Crowther)	3,501,769	Mar. 17, 1970
Gilman et al. (Gilman)	3,538,150	Nov. 3, 1970
Ferrari	3,911,136	Oct. 7, 1975

Ferrini et al. (Ferrini), Arznelm-Forsch, 20(8), 1970, pp. 1074-1079.

Burger (Ed.), Medical Chemistry (New York, Interscience, 1970), 3rd Ed., pp. 1052-1055.

The appealed claims have been rejected under 35 U.S.C. 103 as unpatentable over Crowther, Ferrini and Ferrari considered with Wilhelm, Gilman and Burger. We will not sustain the rejection.

The invention is directed to pharmaceutical compositions containing the levo form of moprolol (1-(o-methoxyphenoxy)-3-isopropylamino-2-propanol) and its use in treating hypertension.

The racemic moprolol being known for the treatment of hypertension by virtue of its β-blocking activity, the knowledge that the levo form would have been expected to be more active and the resolution of the racemic mixture being within the skill of the art and obvious within the meaning of 35 U.S.C. 103 (Appeal No. 591-61, decided August 16, 1985), the claimed compositions and their method of use would have been clearly prima facie obvious.

It is appellants' position that not only does the levo isomer possess double the activity of the racemic mixture (dextro isomer being essentially inactive), the levo isomer also possesses a cardiac stimulant action while the dextro form as well as race-

mic mixture possesses cardiac depressant action. Appellants argue that one would not have expected one of the isomers to possess cardiac stimulant activity while the other, depressant activity. A declaration has been submitted in support of appellant's position.

The examiner, on the other hand, argues that the reduction of the cardiac depressant activity would have been predictably enhanced in the levo form; there being a fine line of difference between enhanced reduction of depressant activity and mild stimulation of said activity. The examiner contends that as the dextro isomer is clearly exerting a negative effect on the racemic mixture; once the racemic mixture is free from the dextro form, observation of the opposite effect (i.e., cardiac stimulant effect) would not have been surprising.

We find the examiner's position is not supported by the evidence of record. Although Ferrini indicates that the myocardial depressant effect of moprolol is about seven times less than that of propranolol, there is no evidence or reason to believe that the levo form, while being a more active hypertensive agent, would possess a cardiac stimulant effect. It does not necessarily follow that a reduction in depressant effect would necessarily result in a stimulant effect. Thus, while one might expect that the levo form would have a reduced depressant effect, there would be no reason to believe that a reduction in the depressant effect would necessarily result in the opposite stimulant effect. While it would appear from the Burger reference that all known β-blockers used in the treatment of hypertension have either a cardiac depressant effect or no effect, nowhere is it seen in the evidence presented that a cardiac stimulant effect had ever been observed or recognized. While the cardiac depressant effect of β-blockers may be desirable in the treatment of certain types of hypertension, the Ferrari declaration indica-

tes that in the treatment of certain types of hypertensive patients there is a need for β-blockers which, as here, possess cardiac stimulant activity. Accordingly, since it would not have been expected that β-blockers of the type involved herein would possess cardiac stimulant activity rather than depressive activity and as there is a particular need in the treatment of specific hypertensive patients with β-blockers with such properties, the prima facie case of obviousness has been rebutted.

In view of the foregoing, the decision of the examiner in rejecting the claims is reversed.

REVERSED

Gordon K. Milestone
Examiner-in-Chief

Melvin Goldstein
Examiner-in-Chief

Mary F. Downey
Examiner-in-Chief

BOARD OF PATENT APPEALS AND INTERFERENCES

Cushman, Darby and Cushman
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SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/163,581	12/7/93	Barberich et al.	SPC8905

08/163,581 12/07/93 BARBERICH T SPC8905

12M1/0726

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EXAMINER	
HENLEY III, R	
R. Henley	
APT UNIT	PAPER NUMBER
1205	39

DATE MAILED 1205

EXAMINER INTERVIEW SUMMARY RECORD

07/26/94

All participants (applicant, applicant's representative, PTO personnel):

(1) Ray Henley (3)

(2) Phil Hansen (4)

Date of interview 13 July 1994

Type: [X] Telephonic [ ] Personal (copy is given to [ ] applicant [ ] applicant's representative).

Exhibit shown or demonstration conducted: [ ] Yes [X] No. If yes, brief description:

Agreement [X] was reached with respect to some or all of the claims in question. [ ] was not reached.

Claims discussed: all, especially 1+6

Identification of prior art discussed: None

Description of the general nature of what was agreed to if an agreement was reached, or any other comments: Copy of Ex Parte Ferrari will be forwarded to Examiner. Examiner's amendment approved.

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendments which would render the claims allowable is available, a summary thereof must be attached.)

Unless the paragraphs below have been checked to indicate to the contrary, A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW (e.g., items 1–7 on the reverse side of this form). If a response to the last Office action has already been filed, then applicant is given one month from this interview date to provide a statement of the substance of the interview.

[ ] It is not necessary for applicant to provide a separate record of the substance of the interview.

[X] Since the examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action.

Examiner's Signature

PTOL-413 (REV. 1-84)

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12M1/0726

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NOTICE OF ALLOWANCE AND ISSUE FEE DUE

☐ Note attached communication from the Examiner
☐ This notice is issued in view of applicant's communication filed _____

SERIES CODE/SERIAL NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT	DATE MAILED
08/163,581	12/07/93	007	HENLEY III, R 1205	07/26/94

First Named Applicant	BARBERICH, TIMOTHY J.

TITLE OF INVENTION: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE (R)-ALBUTEROL

	ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
1	SPC8905	514-649.000	C93	UTILITY	YES	$585.00	10/26/94

THE FEE DUE IS THE AMOUNT IN EFFECT AT THIS TIME. IF THE AMOUNT OF THE ISSUE FEE INCREASES PRIOR TO PAYMENT, APPLICANT WILL BE NOTIFIED OF THE BALANCE OF ISSUE FEE DUE.

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT.

PROSECUTION ON THE MERITS IS CLOSED.

THE ISSUE FEE MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED.

HOW TO RESPOND TO THIS NOTICE:

I. Review the SMALL ENTITY Status shown above.
If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is changed, pay twice the amount of the FEE DUE shown above and notify the patent and Trademark Office of the change in status, or
B. If the Status is the same, pay the FEE DUE shown above.

If the SMALL ENTITY is shown as NO:
A. Pay FEE DUE shown above, or
B. File verified statement of Small Entity Status before, or with, pay of 1/2 the FEE DUE shown above.

II. Part B of this notice should be completed and returned to the Patent and Trademark Office (PTO) with your ISSUE FEE. Even if the ISSUE FEE has already been paid by charge to deposit account, Part B should be completed and returned. If you are charging the ISSUE FEE to your deposit account, Part C of this notice should also be completed and returned.

III. All communications regarding this application must give series code (or filing date) and serial number. Please direct all communications prior to issuance to Box ISSUE FEE unless advised to contrary.

IMPORTANT REMINDER: Patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PATENT AND TRADEMARK OFFICE COPY

DLEV012290

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/163,981	12/07/93	BARBERICH	I SPC3305

EXAMINER
HENLEY III,R

12M1/0726

PHILIP E. HANSEN
HESLIN & ROTHENBERG, P.C.
5 COLUMBIA CIRCLE
ALBANY, NY 12203-5160

ART UNIT	PAPER NUMBER
1205	10

DATE MAILED: 07/26/94

1-22-94

NOTICE OF ALLOWABILITY

PART I.

1. [X] This communication is responsive to the amendment + declaration filed May 11, 1994
2. [X] All the claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice Of Allowance And Issue Fee Due or other appropriate communication will be sent in due course.
3. [X] The allowed claims are 1-6 and 8 (renumbered as 1-7 respectively)
4. [ ] The drawings filed on _____ are acceptable.
5. [ ] Acknowledgment is made of the claim for priority under 35 U.S.C. 119. The certified copy has [_] been received. [_] not been received. [_] been filed in parent application Serial No. _____ filed on _____
6. [X] Note the attached Examiner's Amendment.
7. [X] Note the attached Examiner Interview Summary Record, PTOL-413.
8. [X] Note the attached Examiner's Statement of Reasons for Allowance.
9. [ ] Note the attached NOTICE OF REFERENCES CITED, PTO-892.
10. [ ] Note the attached INFORMATION DISCLOSURE CITATION, PTO-1449.

PART II.

A SHORTENED STATUTORY PERIOD FOR RESPONSE to comply with the requirements noted below is set to EXPIRE THREE MONTHS FROM THE "DATE MAILED" indicated on this form. Failure to timely comply will result in the ABANDONMENT of this application. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

1. [ ] Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION, PTO-152, which discloses that the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.
2. [ ] APPLICANT MUST MAKE THE DRAWING CHANGES INDICATED BELOW IN THE MANNER SET FORTH ON THE REVERSE SIDE OF THIS PAPER.
   a. [ ] Drawing informalities are indicated on the NOTICE RE PATENT DRAWINGS, PTO-948, attached hereto or to Paper No. _____. CORRECTION IS REQUIRED.
   b. [ ] The proposed drawing correction filed on _____ has been approved by the examiner. CORRECTION IS REQUIRED.
   c. [ ] Approved drawing corrections are described by the examiner in the attached EXAMINER'S AMENDMENT. CORRECTION IS REQUIRED.
   d. [ ] Formal drawings are now REQUIRED.

Any response to this letter should include in the upper right hand corner, the following information from the NOTICE OF ALLOWANCE AND ISSUE FEE DUE: ISSUE BATCH NUMBER, DATE OF THE NOTICE OF ALLOWANCE, AND SERIAL NUMBER.

Attachments:
- [X] Examiner's Amendment
- [X] Examiner Interview Summary Record, PTOL-413
- [X] Reasons for Allowance
- [ ] Notice of References Cited, PTO-892
- [ ] Information Disclosure Citation, PTO-1449
- [ ] Notice of Informal Application, PTO-152
- [ ] Notice re Patent Drawings, PTO-948
- [ ] Listing of Bonded Draftsmen
- [ ] Other

RAYMOND E. HENLEY III
PRIMARY EXAMINER
GROUP 120 - ART UNIT 125

PTOL-37 (REV. 4-89) *

USCOMM-DC 80-3789

DLEV012291

EXAMINER'S AMENDMENT/REASONS FOR ALLOWANCE

An Examiner's Amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 C.F.R. § 1.312. To ensure consideration of such an amendment, it **MUST** be submitted no later than the payment of the Issue Fee.

Authorization for this Examiner's Amendment was given in a telephone interview with Philip E. Hansen on July 13, 1994.

The application has been amended as follows:

IN THE CLAIMS:

In claims 1 and 6, line 4, —chronically— has been inserted before the word "administering".

In claim 6, line 3, —chronic administration of racemic— has been inserted before the word "albuterol".

IN THE ABSTRACT:

At the last line, —chronic administration of racemic— has been inserted before the term "albuterol".

The following is an Examiner's Statement of Reasons for Allowance:

Applicants' amendment and the declaration of T. Scott Johnson filed May 11, 1994 have been received, entered and favorably considered. The Examiner agrees

with the statements made by both applicants and the declarant that support exists in the present specification for avoidance of the side effects associated with chronic therapy for asthma. Moreover, it is the Examiner's opinion that it would not have been expected from the prior art of record that the R(-) isomer of albuterol would possess the improved side effect profile as established in the declaration of Dr. Aberg filed July 23, 1993, i.e., that the R(-) isomer of albuterol does not cause the hypersensitivity reaction normally associated with long-term racemic albuterol administration in patients suffering from asthma. This fact is highly significant and compels the Examiner to conclude that the presently claimed invention would not have been obvious under 35 U.S.C. § 103. The Examiner is guided in his opinion by the finding of the Board of Patent Appeals and Interferences in the unpublished decision of Ex parte Ferrari et al. (Appeal No. 629-61) dated January 28, 1987 in which a similar factual situation existed. Further comments relating to this decision as well as the significance of the hypersensitivity reaction associated with racemic albuterol administration, which are hereby adopted by the Examiner, are presented in the paper entitled "Record of Telephonic Interview" filed by applicants on August 5, 1993.

Thus, for the reasons above, claims 1-6 and 8 are deemed to be allowable.

Any comments considered necessary by applicant must be submitted no later than the payment of the Issue Fee and, to avoid processing delays, should preferably accompany the Issue Fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

RAYMOND J. HENLEY III
PATENT EXAMINER
GROUP 120 - ART UNIT 125

PART B—ISSUE FEE TRANSMITTAL

MAILING INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE. Blocks 2 through 6 should be completed where appropriate. All further correspondence including the Issue Fee Receipt, the Patent, advances orders and notification of maintenance fees will be mailed to addressee entered in Block 1 unless you direct otherwise, by: (a) specifying a new correspondence address in Block below; or (b) providing the PTO with a separate "FEE ADDRESS" for maintenance fee notifications with the payment of Issue Fee or thereafter. See reverse for Certificate of Mailing.

PATENT & TRADEMARK OFFICE AUG 5 1994

1. CORRESPONDENCE ADDRESS:

12M1/0726

PHILIP E. HANSEN
HESLIN & ROTHENBERG, P.C.
5 COLUMBIA CIRCLE
ALBANY, NY 12203-5160

2. INVENTOR(S) ADDRESS CHANGE (Complete only if there is a change)

INVENTOR'S NAME

Street Address

City, State and ZIP Code

CO-INVENTOR'S NAME

Street Address

City, State and ZIP Code

☐ Check if additional changes are on reverse side

SERIES CODE/SERIAL NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP/ART UNIT	DATE MAILED
08/163,581	12/07/93	007	HENLEY III, R 1205	07/26/

First Named Applicant: BARBERICH, TIMOTHY J.

TITLE OF INVENTION: METHOD FOR TREATING ASTHMA USING UPTICALLY PURE (R)-ALBUTEROL

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
SEC2905	514-649.000	093	UTILITY	YES	$585.00	10/26/

3. Correspondence address change (Complete only if there is a change)

4. For printing on the patent front page, list the names of not more than 3 registered patent attorneys or agents OR alternatively, the name of a firm having as a member a registered attorney or agent. If no name is listed, no name will be printed.

1 Heslin & Rothenberg, P
2
3

DO NOT USE THIS SPACE

100 MG 08/11/94 08163581 1 242 585.00 CK
100 MG 08/11/94 08163581 1 561 30.00 CK

5. ASSIGNMENT DATA TO BE PRINTED ON THE PATENT (print or type)

(1) NAME OF ASSIGNEE: Sepracor, Inc.

(2) ADDRESS: (CITY & STATE OR COUNTRY) Marlborough, Massachusetts

(3) STATE OF INCORPORATION: IF ASSIGNEE IS A CORPORATION: Delaware

A. ☐ This application is NOT assigned.
☐ Assignment is being previously submitted to the Patent and Trademark Office.
☐ Assignment is being submitted under separate cover. Assignments should be directed to Box ASSIGNMENTS.
PLEASE NOTE: Unless an assignee is identified in Block 5, no assignee data will appear on the patent. Inclusion of assignee data is only appropriate when an assignment has been previously submitted to the PTO or is being submitted under separate cover. Completion of this form is NOT a substitute for filing an assignment.

6a. The following fees are enclosed:
☒ Issue Fee ☐ Advanced Order - # of Copies 10 (Minimum of 10)

6b. The following fees should be charged to:
DEPOSIT ACCOUNT NUMBER 08-1935
(ENCLOSED PART C)
☐ Issue Fee ☐ Advanced Order - # of Copies (Minimum of 10)
☒ Any Deficiencies in Enclosed Fees

The COMMISSIONER OF PATENTS AND TRADEMARKS is requested to apply the Issue Fee to the application identified above.

(Signature of Party in Interest of record) (Date) 8/3/94

NOTE: The Issue Fee will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the Patent and Trademark Office.

TRANSMIT THIS FORM WITH FEE-CERTIFICATE OF MAILING ON REVERSE

DLEV012294

Certificate of Mailing

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to:

Box ISSUE FEE
Commissioner of Patents and Trademarks
Washington, D.C. 20231

on August 3, 1994
(Date)

(Signature)

Philip E. Hansen
(Typed or Printed Name)

August 3, 1994
(Date)

Note: If this certificate of mailing is used, it can only be used to transmit the Issue Fee. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing.

This form is estimated to take 20 minutes to Complete. Time will vary depending upon the needs of the individual applicant. Any comments on the amount of time you require to complete this form should be sent to the Office of Management and Organization, Patent and Trademark Office, Washington, D.C. 20231 and to the Office of Information and Regulatory Affairs, Office of Management and Budget, Washington, D.C. 20503.

REVERSE PTOL-85B (REV. 7-92)(OMB Clearance is pending)

PTO UTILITY GRANT
Paper Number 4/1

The United States of America

The Commissioner of Patents and Trademarks

Has received an application for a patent for a new and useful invention. The title and description of the invention are enclosed. The requirements of law have been complied with, and it has been determined that a patent on the invention shall be granted under the law.

Therefore, this

United States Patent

Grants to the person or persons having title to this patent the right to exclude others from making, using or selling the invention throughout the United States of America for the term of seventeen years from the date of this patent, subject to the payment of maintenance fees as provided by law.

Bruce Lehman

Commissioner of Patents and Trademarks

Marjorie V. Turner

Attest

PTO-1584

(RIGHT INSIDE)

DLEV012296

PETITIONS-OLO

BOX PATENT EXT.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Atty. Docket No. 046714/0113

In re: U.S. Patent No. 5,362,755

Patentee: Timothy J. BARBERICH, *et al.*

Assignee: Sepracor, Inc.

Issue Date: November 8, 1994

REQUEST FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Commissioner of Patents and Trademarks
Washington, D.C. 20231
BOX PATENT EXT.

Sir:

Pursuant to Section 201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984, 35 U.S.C. § 156, Sepracor, Inc. ("Sepracor"), represents that it is the owner of record of United States Patent No. 5,362,755 and hereby requests an extension of the patent term of U.S. Patent No. 5,362,755.

The following information is submitted in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. §1.740, and follows the format and requirements set forth in 37 C.F.R. § 1.740.

(1) "A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics." 37 C.F.R. §1.74(a)(1)

The approved product is XOPENEX™ (Levalbuterol hydrochloride), inhalation solution. The generic name for the approved product is levalbuterol hydrochloride, which is indicated for the treatment or prevention of bronchospasm in adults and adolescents with reversible obstructive airway disease. Synonyms for Levalbuterol hydrochloride are:

(-)-Albuterol hydrochloride;

(R)-Albuterol hydrochloride;

Levosalbutamol hydrochloride

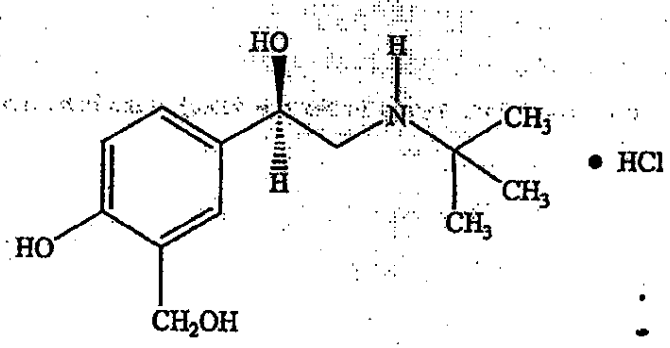
(R)- Salbutamol hydrochloride.

(-)-Salbutamol hydrochloride and

(R)-(-)-Salbutamol hydrochloride.

The Levalbuterol HCl is identified by the following:

(a) Structural Formula:



(b) Chemical Names:

(R)-α^1-[[(1,1-dimethylethyl)amino]methyl]-4-hydroxy-1,3-benzenedimethanol hydrochloride;

α^1-((tert-butylamino)methyl)-4-hydroxy-m-xylene-α,α^1-diol hydrochloride; and

(α^1R)-α^1-[[(1,1-dimethylethyl)amino]methyl]-4-hydroxy-1,3-benzenedimethanol hydrochloride.

(c) Molecular Weight: 275.8

(d) Empirical Formula: $C_{13}H_{21}NO_3 \bullet HCl$

(2) **"A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred, " 37 C.F.R. § 1.740(a)(2).**

Section 505 of the Federal Food, Drug, and Cosmetic Act (FDC Act), 21 U.S.C. § 355, is the Federal statute under which the Food and Drug Administration's (FDA's) regulatory review of Sepracor, Inc.'s XOPENEX™ new drug application (NDA) for Levalbuterol hydrochloride occurred. Section 505(b) of the FDC Act, 21 U.S.C. § 355(b), authorizes the filing of an NDA for a "new drug." FDA subsequently approved the XOPENEX™ NDA (NDA 20,837) under the authority granted the agency by Section 505(c) of the FDC Act, 21 U.S.C. & 355 (c).

(3) **"An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred," 37 C.F.R. § 1.740(a)(3).**

On March 25, 1999, the FDA approved Sepracor's XOPENEX™ (Levalbuterol hydrochloride) NDA under section 505 of the FDC Act. Approval of the NDA authorizes the first commercial marketing of Levalbuterol hydrochloride.

(4) **"In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved," 37 C.F.R. § 1.740(a)(4).**

The active ingredient in Levalbuterol hydrochloride Inhalation Solution is levalbuterol. Levalbuterol has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act the Public Health Service Act or the Virus-Serum-Toxin Act. Levalbuterol is the levorotatory enantiomer of the racemic mixture albuterol. Albuterol has been previously approved by the FDA.

The U.S. Patent and Trademark Office and the Food and Drug Administration have taken the position that an enantiomer has not been "previously approved" for commercial marketing or use by the FDA although the racemate has been previously approved by the FDA. This is shown in the attached letters of communication between the U.S. Patent and Trademark Office (USPTO) and the Food and Drug Administration that determined that the approval of dexfenfluramine hydrochloride was considered to be the first permitted commercial marketing or use of the approved product, although the racemate fenfluramine had been previously approved. (Exhibit F). The July 10, 1996, letter from Hiram Bernstein of the USPTO Office of the Deputy Assistant Comissioner for Patent Policy and Projects to Ronald L. Wilson at the FDA and a response from Mr. Wilson dated November 21, 1996, to Stephen G. Kunin in that same office of the USPTO, show that the approval of the dexfenfluramine hydrochloride enantiomer was determined to be the first permitted commercial marketing or use of the enantiomer product.

(5) "A statement that the application is being submitted within the sixty day period permitted for submission pursuant to § 1.720(f) and an identification of the last day on which the application could be submitted," 37 C.F.R. § 1.740(a)(5)

This application is being submitted within the sixty day period following FDA approval of the XOPENEX™ (Levalbuterol hydrochloride) NDA. FDA approved the XOPENEX™ (Levalbuterol hydrochloride) on March 25, 1999. The sixty day period for submission of this patent extension application will expire on May 24, 1999.

(6) "A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration," 37 C.F.R. § 1.740(a)(6).

U.S. Patent No.	5,362,755
Inventor:	Timothy J. Barberich
Issue Date:	November 8, 1994
Expiration Date:	November 8, 2011

(7) "A copy of the patent for which an extension is being sought including the entire specification (including claims) and drawings," 37 C.F.R. § 1.740(a)(7).

A copy of U.S. Patent 5,362,755 is attached as Exhibit A.

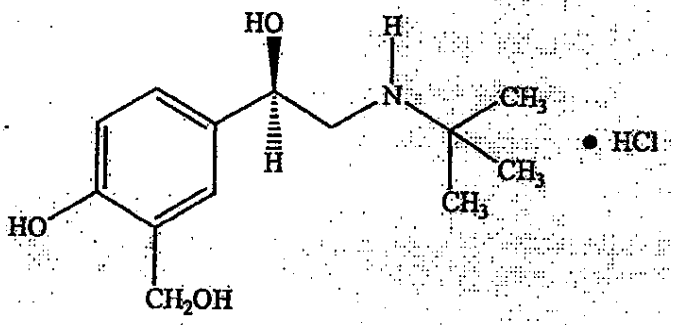
(8) "A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or re-examination certificate issued in the patent," 37 C.F.R. § 1.740(a)(8).

U.S. Patent 5,362,755 issued on November 8, 1994 and the first maintenance fee was paid May 6, 1998. A copy of the printout of the Maintenance Status showing the payment is attached as Exhibit B.

No disclaimer, certificate of correction or re-examination certificate has issued in connection with U.S. Patent No. 5,362,755.

(9) "A statement that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which each applicable patent claim reads on the approved product or method of using or manufacturing the approved product," 37 C.F.R. § 1.740(a)(9).

U.S. Patent No. 5,362,755 claims a method of using the approved product levalbuterol hydrochloride. U.S. Patent No. 5,362,755 claims the approved indication for using levalbuterol hydrochloride. Claims 1, 2, 3, 6 and 7 are directed to the approved method of using levalbuterol hydrochloride for treating an individual with asthma. Levalbuterol hydrochloride is a pharmaceutically acceptable salt of (R)-α^1-[[(1,1-dimethylethyl)amino]methyl]-4-hydroxy-1,3-benzenedimethanol hydrochloride and has the following formula:



Representative claims from U.S. Patent 5,362,755 are reproduced below.

1. A method of treating asthma in an individual with albuterol, while reducing side effects associated with chronic administration of racemic albuterol, comprising chronically administering to the individual a quantity of an optically pure R(-) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects, said R isomer being substantially free of its S(+) isomer.

2. A method of claim 1 wherein the amount of the R(-) isomer of albuterol is greater than approximately 90% by weight of total albuterol.

3. A method of claim 2 wherein the amount of the R(-) isomer of albuterol is greater than 99% by weight of total albuterol.

6. A method of treating asthma in an individual with albuterol, while reducing side effects associated with chronic administration or racemic albuterol, comprising chronically administering to the individual a quantity of an optically pure R(-) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects and at least one additional drug selected from the group consisting of bronchodilators, antihistamines and analgesics.

7. A method of claim 6 wherein the analgesic is selected from the group consisting of: aspirin, acetaminophen and ibuprofen.

The labeling approved by the FDA for Levalbuterol hydrochloride Inhalation Solution, which is marketed under the trade name Xopenex™, states that the drug is "indicated for the treatment or prevention of bronchospasm in adults and adolescents 12 years of age and older with reversible obstructive airway disease." The Clinical Pharmacology section of the FDA approved labeling includes a statement that "Levalbuterol acts as a functional antagonist to relax the airway irrespective of the spasmogen involved, thus protecting against all bronchoconstrictor challenges."

The Drug Interaction section of the FDA approved labeling includes a statement that "[o]ther short-acting sympathomimetic aerosol bronchodilators or epinephrine should be used with caution with levalbuterol." The labeling listed the following drugs to be used with

caution if added to levalbuterol HCl: (1) adrenergic drugs; (2) beta-adrenergic receptor blocking agents; (3) non-potassium sparing diuretics and (4) digoxin. Both claims 6 and 7 cover a condition of use that is included within the approved indication for Xopenex™ when (a) at least one additional drug selected from the group of bronchodilators, antihistamines and analgesics is added to the levalbuterol or (b) an adrenergic drug, a beta-adrenergic receptor blocking agent; a non-potassium sparing diuretic or digoxin is added to levalbuterol HCl with caution.

(10) "A statement, beginning on a new page, of the relevant dates and information pursuant to 35 U.S.C. § 156(g) in order to enable the Secretary of Health and Human Services . . . to determine the applicable regulatory review period . . . For a patent claiming a human drug . . . the effective date of the investigational new drug (IND) application and the IND number; the date on which a new drug application (NDA) . . . was initially submitted and the NDA . . . number and the date on which the NDA was approved" 37 C.F.R. § 1.740(a)(10)(i).

In order to enable the Secretary to determine the applicable regulatory review period, the following information is provided.

(a) Sepracor, Inc. filed its Investigational New Drug (IND) application on February 28, 1995, for XOPENEX™ (Levalbuterol hydrochloride) and it became effective on March 30, 1995.

(b) Sepracor, Inc. initially submitted a new drug application (NDA) for XOPENEX™ (Levalbuterol hydrochloride) to the FDA on June 30, 1997, where it was received on July 1, 1997.

(c) XOPENEX™ (Levalbuterol hydrochloride) was approved by the FDA on March 25, 1999.

(11) "A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities" 37 C.F.R. § 1.740(a)(11).

Attached is a chronology that briefly describes the significant regulatory activities and relevant dates associated with Sepracor, Inc.'s efforts to seek approval of this product before the FDA (Exhibit C).

(12) "A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of the extension claimed, including how the length of extension was determined," 37 C.F.R. § 1.740(a)(12).

Statement of Eligibility of the Patent for Extension

(i) It is the opinion of the applicant that U.S. Patent 5,362,755 is eligible for an extension. This opinion is based on the following information on U.S. Patent No. 5,362,755:

(a) 35 U.S.C. § 156(a) - U.S. Patent No. 5,362,755 claims the approved human drug product XOPENEX™ (Levalbuterol hydrochloride).

(b) 35 U.S.C. § 156 (a)(1) - The term of the patent has not expired prior to the submission of this application.

(c) 35 U.S.C. § 156 (a)(2) - The term of said patent has never been previously extended under 35 U.S.C. § 156 (e)(1).

(d) This application for extension is in compliance with 37 C.F.R. § 1.740.

(e) 35 U.S.C. § 156(a)(4) - The product, XOPENEX™ (Levalbuterol hydrochloride), has been subject to a regulatory review period as defined in 35 U.S.C. § 156(g) before its commercial marketing or use.

(f) 35 U.S.C. § 156(a)(5)(A) - The product received permission for commercial marketing or use under the provision of law (i.e., FDC Act § 505) under which the applicable regulatory review occurred.

(g) The application has been submitted within sixty days from the March 25, 1999, approval date.

(h) 35 U.S.C. § 156(c)(4) - No other patent term has been extended for the same regulatory review period for this product.

Statement as to Length of Extension Claimed

The term of U.S. Patent No. 5,362,755 should be extended by 1 year, 137 days, or until March 25, 2013. This term of extension was determined on the following bases.

First, the following calculation of the regulatory review period is in accordance with 35 U.S.C. § 156 and 37 C.F.R. § 1.775. The length of this extension was determined as follows:

(A) The effective date of the Investigational New Drug (IND) application is March 30, 1995, which was thirty days after FDA receipt of the IND on February 28, 1995. The IND number is 47,303.

(B) The new drug application (NDA) for XOPENEX™ (NDA 20-837) was initially submitted to the FDA on June 30, 1997 and received by the FDA on July 1, 1997.

(C) The NDA was approved by the FDA on March 25, 1999.

(D) U.S. Patent No. 5,362,755 was issued on November 8, 1994, and is entitled to a patent term of 17 years from its issue date.

As set forth in 35 U.S.C. § 156(g)(1)(B), the regulatory review period equals the sum of the following periods (i) and (ii):

> (i) the length of time between the date an exemption under §505(i) of the FFDCA became effective (the effective date of the IND) and the date an application was initially submitted under §505 of the FFDCA (the date of the initial submission of the NDA).

An IND for the product was effective on March 30, 1995. The NDA for the product was submitted on July 1, 1997. Thus, for the purpose of this calculation, item (i) for the product equals the number of days from March 30, 1995, to July 1, 1997, or 824 days.

(ii) the length of time between the date an application was initially submitted under §505(b) of the FFDCA (the date of the initial submission of the NDA) and the date the application was approved (the approval date of the NDA).

The NDA for the product was submitted on July 1, 1997. The NDA was approved on March 25, 1999. Thus, for the purpose of this calculation, item (ii) equals the number of days from July 1, 1997, to March 25, 1999, or 633 days.

In accordance with 35 U.S.C. § 156(c), the term of a patent eligible for extension shall be extended by the time equal to the regulatory review period for the approved product which occurred after the date the patent issued. U.S. Patent No. 5,362,755 issued on November 8, 1994. The entire regulatory review period calculated above occurred after this date.

Second, 35 U.S.C. § 156(c) also sets forth the following exceptions (1) - (3) which may operate to shorten the length of the review period used to calculate patent term extension.

(1) Each period is reduced by any period during which the applicant did not act with due diligence.

There has been no lack of due diligence during the period of regulatory review. Accordingly, no reduction in the review period is required by this provision.

(2) Each period includes only one-half of the number of days in phase (i).

One-half of the number of days in phase (i) equals one-half of 824 days, or 412 days. Adding this number of days to the number of days in phase (ii) (633 days) results in a review period of 1045 days.

(3) If the period remaining in the patent term after the date of approval of the approved product when added to the regulatory review period as revised under paragraphs (1) and (2) above exceeds fourteen years, the period of extension shall be reduced so that the sum of both periods does not exceed fourteen years.

On the date of approval of the product, March 25, 1999, 12 years and 228 days remained in the term of U.S. Patent No. 5,362,755. Adding this period to the review period calculated above yields a period of more than fourteen years. This provision, therefore, shortens the period of extension to which U.S. Patent No. 5,362,755 is entitled, to fourteen years from March 25, 1999, or to March 25, 2013, which represents an extension of 1 year and 137 days.

Third, 35 U.S.C. § 156(g)(6) limits the period of patent term extension to a maximum of five years from the original expiration date of the patent. The original expiration date of U.S. Patent No. 5,362,755 is November 8, 2011. Accordingly, the maximum extension allowed by this provision would extend the term to November 8, 2016. Extension of the patent by the number of days calculated above would not extend the patent beyond November 8, 2016. Accordingly, this provision does not operate to shorten the period of extension to which U.S. Patent No. 5,362,755 is entitled.

Thus, U.S. Patent No. 5,362,755 is entitled to an extension of 1 year and 137 days, to March 25, 2013.

(13) "A statement that applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to any determination of entitlement to the extension sought," 37 C.F.R. § 1.740(a)(13).

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to any determination of entitlement to the extension sought.

(14) "The prescribed fee for receiving and acting upon the application for extension," 37 C.F.R. § 1.740(a)(14).

Pursuant to 37 C.F.R. § 1.20(j)(1), a check in the amount of $1,120.00 is enclosed with this application..

Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of same, the Commissioner is hereby authorized to charge Deposit Account No. 19-0741 for any such fees. Should a refund of fee paid be necessary, the Commissioner is hereby authorized to credit any such amount to Deposit Account No. 19-0741.

(15) "The name, address and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed," 37 C.F.R. § 1.740(a)(15).

Please direct all inquires and correspondence relating to this application for patent term extension to:

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(16) "A duplicate of the application papers, certified as such," 37 C.F.R. § 1.740(a)(16).

Enclosed is a certification that this application for patent extension, including its attachments, is being submitted as one original and one duplicate copy thereof (Exhibit D).

(17) "An oath or Declaration as set forth in 37 C.F.R. § 1.740(b)," 37 C.F.R. § 1.740(a)(ii).

The requisite declaration pursuant to 37 C.F.R. § 1.740(b) is attached as Exhibit E.

Respectfully submitted,

26 May 1999
Date

H. C. Wegner Reg. No. 25,258
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US005362755A

United States Patent [19]

Barberich et al.

[11] Patent Number: 5,362,755

[45] Date of Patent: Nov. 8, 1994

[54] METHOD FOR TREATING ASTHMA USING OPTICALLY PURE (R)-ALBUTEROL

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[73] Assignee: Sepracor, Inc., Marlborough, Mass.

[21] Appl. No.: 163,581

[22] Filed: Dec. 7, 1993

Related U.S. Application Data

[63] Continuation of Ser. No. 896,725, Jun. 9, 1992, abandoned, which is a continuation of Ser. No. 461,262, Jan. 5, 1990, abandoned.

[51] Int. Cl.[5] A61K 31/135

[52] U.S. Cl. 514/649; 514/825

[58] Field of Search 514/649, 826

[56] References Cited

FOREIGN PATENT DOCUMENTS

2255503 7/1992 United Kingdom .

OTHER PUBLICATIONS

R. T. Brittain et al., *Br. J. Pharmacol.*, 48:144–147 (1973).

C. J. Hawkins and G. T. Klease, *J. Med. Chemistry*, 16(7):856–857 (1973).

D. Hartley and D. Middlemiss, *J. Med. Chemistry*, 14(9):895 (1971).

C. K. Buckner and P. Abel, *J. Pharmacol. Exp. Ther.*, 189(3):616–625 (1974).

Tan et al., "Analysis of Salbutomol Enantiomers in Human Urine by Chiral High Performance Liquid Chromatography and Preliminary Studies Related to the Stereoselective Disposition Kinetics in Man", *J. Chromatogr.*, 422, 187–95 (1987).

Chemical Abstracts 89:123259m (1978).

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[57] ABSTRACT

The optically pure R(−) isomer of albuterol, which is substantially free of the S(+) isomer, is a potent bronchodilator for relieving the symptoms associated with asthma in individuals. A method is disclosed utilizing the optically pure R(−) isomer of albuterol for treating asthma while minimizing the side effects associated with chronic administration of racemic albuterol.

7 Claims, No Drawings

METHOD FOR TREATING ASTHMA USING OPTICALLY PURE (R)-ALBUTEROL

This application is a continuation of application Ser. No. 07/896,725 filed Jun. 9, 1992 now abandoned which is a continuation of copending application Ser. No. 07/461,262 filed on Jan. 5, 1990 now abandoned.

DESCRIPTION

1. Background

Albuterol is a drug belonging to the general class of beta-adrenergic compounds. The prime action of beta-adrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (AMP) from adenosine triphosphate (ATP). The cyclic AMP formed mediates the cellular responses. Albuterol acts selectively on beta$_2$-adrenergic receptors to relax smooth muscle tissue, for example, in the bronchial system. Albuterol is most commonly used to treat bronchial spasms associated with asthma and is the active component in well-known commercial bronchodilators such as Proventil and Ventolin.

The form in which albuterol is presently used is a racemic mixture. That is, it is a mixture of optical isomers, called enantiomers. Enantiomers are structurally identical compounds which differ only in that one isomer is a mirror image of the other and the mirror images cannot be superimposed. This phenomenon is known as chirality. Most biological molecules exist as enantiomers and exhibit chirality. Although structurally identical, enantiomers can have profoundly different effects in biological systems: one enantiomer may have a specific biological activity while the other enantiomer has no biological activity at all, or may have an entirely different form of biological activity.

SUMMARY OF THE INVENTION

The present invention relates to a method of treating bronchial disorders, such as asthma, in an individual, by administering to the individual an amount of optically pure R(−) albuterol which is active in bronchial tissue sufficient to reduce bronchial spasms associated with asthma while minimizing side effects associated with albuterol. The method is particularly useful in treating asthma while reducing side effects, such as central nervous system stimulatory effects and cardiac arrythmia. In these applications, it is important to have a composition which is a potent broncho-dilator and which does not exhibit the adverse side effects of many beta-adrenergic drugs. A composition containing the pure R(−) isomer of albuterol is particularly useful for this application because this isomer exhibits these desired characteristics. The present method provides a safe, effective method for treating asthma while reducing undesirable side effects, for example, tremor, nervousness, shakiness, dizziness and increased appetite, and particularly, cardiac arrythmia, typically associated with beta-adrenergic drugs. In children, side effects such as excitement, nervousness and hyperkinesia are reduced when the pure isomer is administered. In addition to the above, at certain levels racemic albuterol can cause teratogenic effects, which are believed to be associated with the S(+) isomer. Administering the pure isomer reduces the teratogenic potential which is associated with the S(+) isomer of albuterol.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relies on the bronchodilation activity of the R(−) enantiomer of albuterol to provide relief from bronchial disorders, while simultaneously reducing undesirable side effects, for example, central nervous system stimulatory effects and cardiac disorders, commonly experienced by albuterol users. In the present method, the optically pure R(−) isomer of albuterol, which is substantially free of the S(+) enantiomer, is administered alone, or in combination with one or more other drug(s) in adjunctive treatment, to an individual in whom asthma relief (e.g., relief from bronchial spasms, shortness of breath) is desired. The optically pure R(−) isomer of albuterol as used herein refers to the levorotatory optically pure isomer of α[(tert-butylamino) methyl]-4-hydroxy-m-xylene-α, α'-diol, and to any biologically acceptable salt or ester thereof. The terms "optically pure" or "substantially free of the S(+) enantiomer" as used herein means that the composition contains at least 90% by weight of the R(−) isomer of albuterol and 10% by weight or less of the S(+) isomer. Optically pure albuterol is readily obtainable by methods known to those of skill in the art, for example, by synthesis from an optically pure intermediate.

In the present method, the R(−) isomer of albuterol is administered to an individual who has asthma. For example, R(−) albuterol is administered to an individual after onset of asthma to reduce breathing difficulty resulting from asthma. In another embodiment, optically pure R(−) albuterol is administered prophylactically, that is, before the bronchiospasm begins in an asthma attack, to prevent its occurrence or to reduce the extent to which it occurs.

In the present method, R(−) albuterol can be administered by inhalation, by subcutaneous or other injection, orally, intravenously, topically, parenterally, transdermally, rectally or via an implanted reservoir containing the drug. The form in which the drug will be administered (e.g., inhalant, powder, tablet, capsule, solution, emulsion) will depend on the route by which it is administered. The quantity of the drug to be administered will be determined on an individual basis, and will be based at least in part on consideration of the individual's size, the severity of the symptoms to be treated and the result sought. In general, quantities of optically pure R(−) albuterol sufficient to reduce the symptoms of asthma will be administered. The actual dosage (quantity administered at a time) and the number of administrations per day will depend on the mode of administration, for example, by inhaler, nebulizer or oral administration. About 30 mcg to about 90 mcg of the optically pure R(−) isomer of albuterol given by inhalation one or more times per day will be adequate in most individuals to produce the desired bronchodilation effect. For oral administration, e.g., tablet or syrup, a dose of about 1 mg to about 8 mg two to four times daily is administered to produce the desired effect.

In the method of the present invention, the optically pure R(−) isomer of albuterol can be administered together with one or more other drug(s). For example, an antiasthmatic drug such as theophylline or terbutaline, or an antihistamine or analgesic such as aspirin, acetaminophen or ibuprofen, can be given with or in close temporal proximity to administration of optically pure, R(−) albuterol. The two (or more) drugs (the

optically pure active isomer of albuterol and another drug) can be administered in one composition or as two separate entities. For example, they can be administered in a single capsule, tablet, powder, or liquid, etc. or as individual compounds. The components included in a particular composition, in addition to optically pure albuterol and another drug or drugs, are determined primarily by the manner in which the composition is to be administered. For example, a composition to be administered in inhalent form can include, in addition to the drug(s), a liquid carrier and/or propellent. A composition to be administered in tablet form can include a filler (e.g., lactose), a binder (e.g., carboxymethyl cellulose, gum arabic, gelatin), an adjuvant, a flavoring agent, a coloring agent and a coating material (e.g., wax or a plasticizer). A composition to be administered in liquid form can include the combination of drugs and, optionally, an emulsifying agent, a flavoring agent and/or a coloring agent.

In general, according to the method of the present invention, the optically pure R(−) isomer of albuterol, alone or in combination with another drug(s), is administered to an individual periodically as necessary to reduce symptoms of asthma.

The present composition and method provide an effective treatment for asthma while minimizing the undesirable side effects associated with albuterol use. These side effects include central nervous system effects, such as tremor, nervousness, shakiness, dizziness and increased appetite, and cardiac effects, such as cardiac arrythmia. In children, side effects, such as excitement, nervousness and hyperkinesia, are reduced when the pure isomer is administered. In addition, teratogenic effects associated with albuterol are believed to reside in the S(+) enantiomer. Thus, administering the pure R(−) isomer may reduce the teratogenic potential associated with albuterol.

Equivalents

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed in the scope of the following claims.

We claim:

1. A method of treating asthma in an individual with albuterol, while reducing side effects associated with chronic administration of racemic albuterol, comprising chronically administering to the individual a quantity of an optically pure R(−) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects, said R isomer being substantially free of its S(+) isomer.

2. A method of claim 1 wherein the amount of the R(−) isomer of albuterol is greater than approximately 90% by weight of total albuterol.

3. A method of claim 2 wherein the amount of the R(−) isomer of albuterol is greater than 99% by weight of total albuterol.

4. A method of claim 1 comprising administering to the individual by inhalation from approximately 30 mcg to approximately 90 mcg of the R(−) isomer of albuterol per dose.

5. A method of claim 1 comprising orally administering to the individual from approximately 1 mg to approximately 8 mg of the R(−) isomer of albuterol two to four times daily.

6. A method of treating asthma in an individual with albuterol, while reducing side effects associated with chronic administration of racemic albuterol, comprising chronically administering to the individual a quantity of an optically pure R(−) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects and at least one additional drug selected from the group consisting of bronchodilators, antihistamines and analgesics.

7. A method of claim 6 wherein the analgesic is selected from the group consisting of: aspirin, acetaminophen and ibuprofen.

* * * * *